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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,922	LISZIEWICZ ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *See "Other" below*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-26,28,30-33,35 and 37-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-26, 28, 30-33, 35 and 37-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other:

The instant office action is in response to the RCE filed 4-13-05 placed in parent application 09/153,198 by mistake because of unclear headings on the response, the arguments filed in the response on 6-13-05, the claims filed by fax on 7-12-05 at 3:32 pm, and the decision to revive sent 8-18-05.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's request for continued examination filed on 4-13-05 has been entered.

The amendment filed by fax on 7-12-05 at 3:32 pm is under consideration in conjunction with the arguments filed 6-13-05.

The amendment filed by fax on 7-12-05 at 5:01 pm, the amendment filed by fax on 7-12-05 at 5:11 pm, and the amendment filed by mail on 7-14-05 are not being considered as they are duplicates of the amendment filed by fax on 7-12-05 at 3:32.

The arguments filed 10-22-04 are not being considered because they appear to be substantially the same as those being considered.

The amendment filed 10-22-04 (moved from parent application 09/153,198) is not being considered because it is identical to the claims filed 6-24-04, which were addressed in the final office action of 9-22-04.

Claims 1-22, 27, 29, 34 and 36 have been canceled. Claim 43 has been added. Claims 23-26, 28, 30-33, 35 and 37-43 are under consideration.

Applicant's arguments filed 6-13-05 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

This application repeats a substantial portion of prior Application No. 09/153198, filed 9-15-98, and claimed additional disclosure not presented in the prior application. Specifically, the preliminary amendment filed with the instant application added claim 23, which required mixing DNA and "a compound selected from the group consisting of sugars, polyethylenimine, polyethylenimine derivatives, or mixtures thereof". Neither 09/153,198 nor the instant disclosure provides support for "mixtures thereof" in this context. While the amendment filed 2-21-02 states claims 23-41 are supported by the original claims, the originally claims do not provide support for combining mixtures of sugar, polyethylenimine and polyethylenimine derivatives, with DNA. However, the limitation of "mixtures thereof" was deleted in the amendment filed 7-12-05. Therefore, this application is a "division" of parent application 09/153,198. The first line of the specification is correct.

Claims 23-26, 28, 30-33, 35 and 37-43 (methods of transuding cells and methods of inducing an immune response in mammals) are patentably distinct invention from the claims in parent application 09/153,198, now US Patent 6,240,176, filed 9-15-98 (products).

Specification

The amendment to the first line of the specification filed 6-7-04 has omitted original text, i.e. reference to "USSN 09/153,198" has been deleted completely without being marked as being deleted. The correct format for the first line is as follows: "This application is a division of US Application 09/153,198, filed 9-15-98, now US Patent 6,420,176, which is a continuation-in-part of...." It is noted that the instant application appears to be a CIP and not a DIV of '198.

The status of the application on pg 9, line 7, will have to be updated as necessary.

The status of applications on pg 17, line 34-38, have been updated.

The status of the application on pg 13, line 36, will need updated as necessary.

The status of the application on pg 18, line 32, will need updated as necessary.

The objection to the amendment filed 2-21-02 under 35 U.S.C. 132 because it introduces new matter has been withdrawn. The sentence added to the paragraph on pg 13, line 26, has support in claim 7 as originally filed.

Claim Objections

The objection to claim 35 has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112

New Matter

The rejection of claims 23-26, 28, 30-33, 35 and 37-42 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention has been withdrawn.

The rejection regarding the phrase "applying the complex to the skin or mucosa of an animal" has been withdrawn because the phrase has support on pg 16, line 34, and claims 17 and 19 as originally filed.

The rejection regarding applying a gene delivery complex to the skin or mucosa of an animal and transfecting any antigen presenting cell (APCs) (claim 23) has been withdrawn. Support is found on pg 2, line 19, for example.

The rejection regarding the phrase "mixtures thereof" (claim 23) has been withdrawn because the phrase has been deleted.

The rejection regarding claim 27 regarding a mannosylated PEI "derived from a linear PEI 22 kDA" has been withdrawn because the claim has been canceled.

The rejection regarding the phrase "3:1-10:1 molar equivalents" (claim 29) has been withdrawn because the claim has been canceled.

The rejection regarding the phrase "about 5-10" (claim 32) and "about 8" (claim 33) has been withdrawn because the term "about" has been deleted.

The rejection regarding applying the complex to the skin or mucosa and further obtaining receptor stimulation, toxin activation, or tissue or cell injury in claim 35 has been withdrawn because support has been found on pg 16, lines 32-38.

The genus of delivering DNA encoding any "at least one immunogenic protein" in claim 23 as newly amended is found on pg 13, lines 19-25.

Support for "electrostatically neutral" in claim 28 can be found on pg 22, lines 3-8.

The limitation of "5:1 molar equivalents" (claim 30) has support on pg 22, line 11.

The limitation of a derivate being a sugar-modified PEI in claim 43 is found on pg 15, line 7.

Written Description

The rejection regarding the phrase "PEI, PEI derivatives and mixtures thereof" in claim 23 has been withdrawn because the phrase "and mixtures thereof" has been deleted.

The rejection regarding applying a gene delivery complex to the skin or mucosa of an animal and transfecting any antigen presenting cell (APCs) (claim 23) has been withdrawn. Support is found on pg 23, Example 9, for example, which teaches transfecting Langerhans cells that migrate to the lymph nodes. In addition, applying a gene delivery complex to the skin or mucosa of an animal results in transfecting various APCs, e.g. macrophages, dendritic cells and B-cells (Condon, Nature Med., 1996, Vol. 2, No. 10, pg 1122-1128; Tuting (J. Invest. Derm., 1998, Vol. 111, pg 183-188).

1. Claims 37-39 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

Claims 37-39 remain rejected under written description because the specification does not describe the structure of the gene delivery complex capable of transfecting APCs such that a therapeutic or prophylactic effect is obtained – the sole disclosed purpose for transfecting APCs disclosed in the specification. Claims 37-39 require applying a gene delivery complex to the skin or mucosa of an animal, wherein the gene delivery complex comprises DNA encoding a protein from HIV (37), from a replication-defective HIV (38), or an integration-defective, replication-defective HIV (39). The only described function for such a method is to treat or prevent HIV infection. The specification does not provide adequate written description for applying a gene delivery complex to the skin or mucosa of an animal, wherein the gene delivery complex comprises DNA encoding an HIV protein such that a therapeutic or prophylactic effect is obtained.

Applicants describe plasmids encoding replication-defective, integrase-defective retroviral DNA in related application 08/989,301 as being non-lethal and capable of inducing a therapeutic/prophylactic immune response when administered in vivo. However, Adachi, of record (J. Virol., Aug. 1986, Vol. 59, pg 284-291), taught such viruses were still infectious. Applicants do not adequately describe DNA encoding a HIV protein that is capable of inducing a therapeutic/prophylactic immune response. Nowhere have applicants provided any evidence that the amount of expression of viral protein is adequate to induce a therapeutic/prophylactic immune response or that the

virus does not replicate too much and cause disease. Use of the plasmids encoding replication-defective retrovirus in animals as claimed would not treat or prevent disease because the virus would replicate and cause disease. Applicants appear to be attempting to find DNA comprising a lentiviral protein that expresses adequate viral protein such that a cellular immune response can be obtained, wherein said DNA i) does not make retroviral particles or ii) does make viral particles that replicate to a low degree without causing disease. Naming a type of material that may exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming a method of using DNA encoding replication-defective retroviral proteins without defining the DNA that will encode adequate amounts of retroviral protein to induce a therapeutic/prophylactic effect without causing retroviral particle formation or retroviral infection is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

The specification suggests using the method claimed to induce an immune response in a mammal (pg 20, Example 4). However, Example 4 does not correlate to the claimed invention because dendritic cells were transfected in vitro and because the gene delivery complex was not applied to the skin or mucosa as claimed. Merely inducing an immune response in a mammal by administering transfected dendritic cells, in and of itself, does not have a function by itself in Example 4 without inducing an immune response as described on (pg 2, lines 20-24; pg 18, lines 2-8). Therefore,

inducing an immune response according to the specification must result in a therapeutic or prophylactic effect to meet the description of the invention in the application as originally filed.

Therefore, the specification does not provide adequate written description for applying a gene delivery complex to the skin or mucosa of an animal, wherein the gene delivery complex comprises DNA encoding an HIV protein such that a therapeutic or prophylactic effect is obtained.

Applicants argue, "the present language is supported on pg 13, lines 27-36" (pg 8 of response). Applicants' argument is not persuasive. Pg 13, lines 27-36, does not address the written description rejections above because it generically relates to DNA encoding a replication or integration defective HIV virus.

Applicants' arguments regarding the case law on pg 8 of response are moot because the case law cited relates to enablement and not written description.

Enablement

The rejection of claims 23-26, 28, 30-33, 35 and 37-42 regarding obtaining a therapeutic effect by applying a gene delivery complex encoding a lentiviral antigen to the skin or mucosa of an animal has been withdrawn because the phrase "wherein the immunogenic protein is from a lentivirus" in claim 23 has been deleted. Methods of applying a gene delivery complex to the skin of an animal, wherein the gene delivery complex comprised DNA encoding an immunogenic protein, were known in the art to have a therapeutic or prophylactic effect. Robinson (Vaccine, 1993, Vol. 11, pg 957-

960) protected against influenza by splitting a dose of plasmid DNA encoding an influenza protein solubilized in saline three ways; one part of the does was injected subcutaneously, one part of the dose was injected intravenously and one part of the dose was injected intraperitoneally. Fynan (PNAS, 1993, Vol. 90, pg 11478-11482) protected against influenza by applying plasmid DNA encoding an influenza protein solubilized in saline intranasally, intradermally, subcutaneously and using gold particles and a gene gun (intradermally) (pg 11479, col. 1, "Vaccine trials" and "Gene gun-delivered DNA"; pg 11479, col. 2, "inoculations of DNA in saline" and pg 11480, col. 1, "Gene-gun delivery of DNA"). Lai (DNA and Cell Biol., 1995, Vol. 14, No. 7, pg 643-651) protected against mycoplasma infection by applying DNA encoding a mycoplasma protein solubilized in gold particles to the ear using a gene gun (pg 645, ¶ bridging col. 1-2; pg 648, "Clinical Observations"). Ma (Acta virologica, 1996, Vol. 40, pg 311-314) protected ducks against HBV by applying vaccinia to the duck intradermally (pg 312, col. 2 "Expression of DHBV Pre-S/S...") and plasmid encoding the Pre-S/S protein intradermally (pg 312, col. 2, "Immunization of persistently DHBV-infected ducks with pGDBHV-5...).

The rejection regarding the scope of antigen presenting cell (APCs) transfected by applying a gene delivery complex to the skin or mucosa of an animal as claimed has been withdrawn because pg 23, Example 9, shows transfecting Langerhans cells that migrate to the lymph nodes and because applying a gene delivery complex to the skin or mucosa of an animal results in transfecting various APCs, e.g. macrophages,

dendritic cells and B-cells (Condon, Nature Med., 1996, Vol. 2, No. 10, pg 1122-1128; Tuting (J. Invest. Derm., 1998, Vol. 111, pg 183-188).

2. Claims 37-39 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

Claims 37-39 are not enabled because the specification does not provide adequate guidance for one of skill to induce a therapeutic or prophylactic immune response by applying a gene delivery complex encoding HIV to the skin or mucosa of an animal.

Claims 37-39 require applying a gene delivery complex to the skin or mucosa of an animal, wherein the complex comprises i) DNA encoding an immunogenic protein operably linked to a promoter; and ii) sugar, polyethylenimine (PEI), a PEI derivative, wherein the protein is from HIV (37), a replication-defective HIV (38), or an integration-defective, replication-defective HIV (39).

The specification describes using the method claimed to induce an immune response in a mammal (pg 20, Example 4). However, merely inducing an immune response in a mammal, in and of itself, does not have an enabled use because inducing an immune response is only described in the specification as being used to obtain a therapeutic or prophylactic effect (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, inducing an immune response against HIV according to the specification must result in

a therapeutic or prophylactic effect to have an enabled use. The ordinary artisan reading claims 37-39 in view of the specification would determine that the methods were only used for therapy or prophylaxis. Enablement rejection b) is based on the sole disclosed use for the methods of claims 37-39 - therapy or prophylaxis.

Klatzmann and Sticker taught retroviral vaccines have been unable to protect against infection (Klatzmann, US Patent 6,140,114, Oct. 31, 2000; Stricker, Medical Hypotheses, June 1997, Vol. 48, pg 527-9, both of record). Overall, a lack of understanding about protective immunity to retroviruses such as HIV, the sequence variability and the rapid replication of retroviruses contribute the ineffectiveness of vaccines against retroviruses (Bangham, of record, Nov. 29, 1997, Lancet, Vol. 350, pg 1617-1621; pg 1617, top of col. 1).

The specification teaches making plasmids encoding replication defective, integrase-defective HIV as described in application 08/989,301 (pg 18, line 30-32). In application 08/939,301, applicants call such retroviruses "Class 4" viruses that are infectious but replication-defective (pg 15, lines 1-5). In application 08/989301, applicants teach that replication defective HIV that does not replicate effectively is inadequate to elicit a protective cellular immune response. Alternatively, replication defective HIV that does replicate effectively causes disease and sometimes fatal (pg 3, line 17 through pg 4, line 3). The amount of replication of a retrovirus required to obtain a therapeutic cellular immune response without causing disease was unknown in the art at the time of filing. It was also unknown how to make a retrovirus with the adequate amount of replication that would provide an adequate cellular immune response without

causing disease. Without being able to make such a retrovirus, it was unknown how to use such a virus to obtain a therapeutic or prophylactic cellular immune response in a host.

The specification does not provide adequate guidance regarding how to obtain a therapeutic or prophylactic effect by applying a replication defective retrovirus in an animal as claimed. The specification does not teach the amount of a cellular immune response that is therapeutic or prophylactic effect against a replication defective retrovirus. The amount of dendritic cells required to obtain adequate antigen presentation is not provided in the specification. The amount of retroviral protein expression required to obtain the desired cellular immune response is not provided in the specification. The amount of replication and infectiousness required to obtain the desired balance between therapy and pathogenicity is not provided in the specification. Given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine how to make and/or use a replication defective retrovirus to obtain a therapeutic/prophylactic effect without causing disease or death.

In addition, it was unpredictable what vector, promoter, dosage, cells, level of expression and route of administration would provide a therapeutic or prophylactic effect using *in vivo* or *ex vivo* gene therapy (Miller 1995, FASEB J., Vol. 9, pg 190-199; pg 198, col. 1; Deonarain, 1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69; pg 53, 1st ¶, pg 65, 1st ¶ under Conclusion section; Verma, Sept. 1997, Nature, Vol. 389, pg 239-242; see entire article, specifically pg 240, sentence bridging col. 2 and 3; Crystal, 1995,

Science, Vol. 270, pg 404-410, pg 409; Ross, Sept. 1996, Human Gene Therapy, Vol. 7, pg 1781-1790; pg 1782, col. 2, 1st full ¶; pg 1789, col. 1, 1st ¶, all of record).

The specification does not enable applying DNA encoding a lentiviral protein to the skin or mucosa to transfect APCs and obtain a therapuetic or prophylactic effect. The specification does not teach applying DNA to the mucosa results transfection of APCs or in expression of the protein in the APCs. The specification does not teach the amount of lentiviral protein expression required for the APCs to present adequate antigens to the immune system such that a therapuetic/prophylactic immune response is obtained. The specification does not teach the immune response to a lentiviral antigen required to treat or prevent disease. The specification does not provide the combination of vector, promoter, dosage, level of expression that would result in a therapeutic/prophylactic effect. Given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine the vector, promoter, cell, dosage, level of expression and route of administration required to obtain a therapeutic or prophylactic effect using the method claimed.

Applicants argue the Examiner has not correctly stated the applicable law, but applicants have not pointed to any specific error. Applicants imply the Examiner has attempted to evade the instruction received from the Federal Circuit, but the case law cited by applicants does not apply. Applicants' arguments are not persuasive because the examiner has cited the law under 112/1st paragraph regarding enablement and has

addressed all standards for enablement (i.e. the Wands factors, the state of the art, the skill level of those in the art) discussed in case law relating to enablement.

Applicants argue that the Examiner's interpretation of the claimed invention as being limited to a method of transfection APCs by applying the complex to the skin or mucosa of an animal for the purpose of therapy or prophylaxis is in error because the claims merely require transfecting APCs and do not require a step in which therapy or prophylaxis is obtained. Applicants' argument remains unpersuasive. The claims must be read in light of the specification. The only purpose for applying DNA encoding an immunogenic protein to the skin or mucosa of an animal is for therapy or prophylaxis. Pg 13, lines 19-25, states:

"If the purpose of the gene transfer is to induce an immune response, then the genetic material must express one or more immunogenic proteins. Transduced cells will subsequently express enough of the immunogenic proteins (different viral antigens and produce authentic enough viral particles) to provoke a sufficient immune response (e.g., protect the individual from infection by the wild-type virus)."

When reading the claims in light of the spec, merely applying DNA encoding an immunogenic protein to the skin or mucosa of an animal (or even adding the optional phrase "transfecting APCs" in the preamble) without obtaining a therapeutic or prophylactic effect does not have a disclosed or enabled use and has no meaning. Therefore, it is reasonable to interpret the claimed methods as only being used for treatment or prophylaxis and to determine whether applicants have provided adequate guidance for that one disclosed use, i.e. whether applicants provide adequate guidance

for those skilled in the art to apply DNA encoding an immunogenic protein to the skin or mucosa of an animal and obtain therapy or prophylaxis. As such, the method claims (having only one disclosed use without specifically reciting the one disclosed) remain rejected under enablement because their one disclosed use has not been enabled.

Applicants argue the *in vitro* data described by applicants enables the invention. Applicants argument is not persuasive. The claims require applying the complex to the skin or mucosa of an animal; therefore, the claims are limited to transfecting cells *in vivo*. The *in vitro* data does not correlate to *in vivo* data for reasons cited above because the only disclosed use for performing the method *in vivo* is to obtain an immune response against the immunogenic protein that is therapuetic or prophylactic. However, HIV patients have a CTL response to HIV proteins that is not therapeutic or prophylactic. Furthermore, the immune response required to treat or prevent lentiviral infection was not known (see references of record above). Thus, the art was and continues to be completely absence of methods to treat or prevent lentiviral infection *in vivo* using by inducing an immune response. Therefore, data showing that APCs can be transfected *in vitro* using a gene delivery complex as claimed cannot support using the claimed method to treat or prevent disease.

Applicants argue the *in vivo* data described by applicants enables the invention. Applicants provide Lisziewicz (J. Invest. Derm., Jan. 2005, Vol. 124, No. 1, pg 160-169 (which is equivalent to the Lisziewicz, 2004, reference provided by applicants, but not found elsewhere)) who taught using DermaVir to make particles containing DNA, PEIm and glucose and administering the comlex on about 40 cm2 skin at four locations: the

left and right upper inguinal region and left and right axialllary region for 30 minutes (pg 167, col. 1, "Topical and *ex vivo* DermaVir immunization"). Applicants argument is not persuasive.

DermaVir, described in Lisziewicz (2005) is not disclosed in the instant application. The structure of DermaVir is not described by Lisziewicz (2005) but is "formulated to make a approximately 100 nm particle containing DNA, PEIm, and glucose" (pg 167, col. 1, "Topical and *ex vivo* DermaVir Immunization" of Lisziewicz (2005)). Lisziewicz (2005) states DermaVir was used in Lisziewicz (2001, of record); however, Lisziewicz (2001) described using PEI or PEI-mannose to deliver DNA (at a 5:1 ratio) without using glucose. Thus, DermaVir, mentioned by Lisziewicz in 2005, was used to make gene delivery particles containing DNA, PEIm and glucose; however, the structure of DermaVir was not described in Lisziewicz (2005). Therefore, the gene delivery complex described by Lisziewicz (2005) does not correlate to the instant application because it teaches more than the original disclosure (DermaVir). The instant application does not describe the structure of DermaVir which may be essential to the invention. As such, Lisziewicz (2005) cannot be relied upon for enablement of the instant application because it uses DermaVir, which was not disclosed in the instant application.

Furthermore, Lisziewicz (2005) is limited to particles containing plasmid DNA, PEI-mannose and glucose (pg 166, col. 2, 1st full ¶), which is much narrower than the claimed invention. Therefore, the limited species of gene complex of Lisziewicz (2005)

cannot be relied upon for enablement of the broader genus of gene delivery complex used in the method of claim 23.

Finally, Lisziewicz (2005) does not enable one of skill to use the gene delivery complex to obtain a therapeutic or prophylactic effect. Inducing an HIV-specific immune response in vivo against a lentiviral protein failed to provide a therapeutic or prophylactic effect (Lori, Current Meical and Chemical Anti-Infective Agents, 2004, Vol. 3, pg 31-41; pg 31, col. 1, 2nd ¶, lines 7-10). Ready (Nature Medicine, (April 2003, Vol. 9, No. 4, pg 376) clearly states that HIV vaccines capable of preventing infections in humans was not predictable (col. 1, last full ¶) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). Applicants have not provided any evidence or any reasonable explanation that the claimed method overcomes such unpredictability so that an adequate immune response would be induced and a therapeutic or prophylactic effect obtained. Without such guidance, inducing CD4 helper and CD8 cells as described by Lisziewicz (2005) is not adequate to enable using the claimed invention to obtain a therapeutic or prophylactic effect.

The examiner is not requiring a showing or exemplification of inducing a therapuetic or prophylactic immune response using the method claimed; rather, the examiner is requiring a showing or exemplification of inducing a therapuetic or prophylactic immune response using the method claimed or a reasonable teaching of how to overcome the unpredictability in the art, i.e. the amount and type of protein to be expressed, the combination of promoter, protein and vector required to obtain adequate amounts of protein expression upon being applied to the skin or mucosa, how to

adequately target the proper number of APCs by applying DNA to the skin or mucosa, the proper number of APCs to be targeted and the immune response required to treat or prevent lentiviral infection. In this case, applicants have provided neither a showing or a reasonable correlation.

Applicants arguments regarding Animal Legal Defense Fund vs Quigg, 18 USPQ 2d 1677, 1685, Fed. Cir. (1985) (pg 6 and pg 12 of response) are moot because the case relates to utility under 101 and not enablement. The case law also relates to animals and not to methods of applying a DNA complex to an animal as claimed in the instant application.

Applicants arguments regading Radomex vs Scopus Corp. (pg 6 and pg 12 of response) are also moot because the examiner has taken the level of skill into account throughout the enablement rejection.

Applicants argument regarding Lindeman Maschinenfabrik GmbH v American Hoist & Derrick Co. is misplaced because it relates to establishing what was known at the time of filing. The examiner has provided numerous references regarding what was known about using HIV vaccines to treat or prevent disease.

Applicants cite other case law on pg 7 and 12 of the response but fail to correlate the case law to the claimed invention. The case law on pg 7 and 12 has been reviewed but is misplaced because they relate to 101 rejections and to Wands factors that have been specifically addressed by the examiner.

Again, applicants erroneously state the examiner is requiring a showing of a therapeutic or prophylactic effect (pg 7, 1st full ¶). Instead, the examiner is requiring

either a showing of a therapeutic or prophylactic effect or a reasonable teaching so that one of skill would be able to overcome the art established unpredictability that persists to this day. Neither has been fulfilled in this case.

Applicants state "Klatzmann and Stickler relate to retroviral vaccines (not DNA) of others in totally different methods of gene delivery, and demonstrated failure of others" (pg 13, lines 1-8 of response). Applicants' argument cannot be determined. The Klatzmann and Stickler establishes that the lack of understanding about protective immunity to retroviruses such as HIV, the sequence variability and the rapid replication of retroviruses contribute the ineffectiveness of vaccines against retroviruses. As such, Klatzmann and Stickler establish that treating or preventing HIV using a vaccine – even DNA encoding an HIV protein as claimed - requires knowledge of the protective immunity required to treat or prevent HIV or to overcome the sequence variability of HIV. Therefore, the teachings of Klatzmann and Stickler clearly relate to any composition used to treat or prevent HIV infection. Applicants fail to overcome the teachings of Klatzmann and Stickler, both of record, and Lori and Ready, both provided in the instant office action, by teaching the protective immunity required to treat or prevent HIV or how to adapt the method to the sequence variability of HIV.

Indefiniteness

The rejection of claim 23 regarding "mixtures thereof" has been withdrawn because the phrase has been deleted.

The rejections regarding claim 27 has been withdrawn because the claim has been canceled.

The rejection regarding claim 29 regarding the phrases "3:1-10:1 molar equivalent of either polyethylenimine or polyethylenimine derivative amine per molar equivalent of DNA phosphate" has been withdrawn because the claim has been canceled.

The rejection regarding "about" in claims 32 and 33 has been withdrawn because the term was deleted in the amendment filed previously.

The rejection of claim 34 regarding the phrase "activating the antigen presenting cells" has been withdrawn because the claim has been canceled.

The rejection regarding the metes and bounds of what applicants consider "activating" APCs in claim 35 has been withdrawn because the phrase "wherein the activating step" has been deleted.

The rejection regarding the metes and bounds of what applicants consider a "reverse transcriptase dependent virus" (claims 36 and 37) has been withdrawn because claim 36 has been cancelled and the phrase has been deleted from claim 37.

3. Claims 23-26, 28, 30-33, 35, 37-42 remain rejected and claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 23 remains indefinite because the body of the claim merely requires applying a complex to the skin or mucosa surface of an animal but the preamble requires transduction of APCs. The body of the claim never obtains transfection of APCs or expression of the protein in APCs. Thus, the preamble and the body of the claim do not have a nexus making the claim as a whole unclear.

Claim 23 remains indefinite because it is unclear if "transfecting" is limited to transfection with plasmid or if the term encompasses infection with a viral particle. The specification does not define "transfection". Applicants argue the term was inserted "to comply with what they thought was a demand by the examiner." Applicants state they are open to suggestions but do not provide any suggestions or any other arguments. Applicants' arguments are not substantive. The examiner merely rejected the previous term "transducing" under 112/2nd in the office action of 3-10-04.

Claim 23 remains indefinite because the metes and bounds of what applicants consider "applying" to the skin cannot be determined. It is unclear if the phrase is limited to putting the complex on the skin or if the phrase encompasses subcutaneous injection which results in delivery of the complex under the skin. It is unclear if intravenous injection is encompassed by the phrase because such an injection does require contact of the complex to the skin when the injection passes through the skin. Applicants argue the phrase has support on pg "16, line 34, where application to the skin is distinguished from injection." Applicants' argument is not persuasive. Pg 16, line 34, merely states, "The complex can be applied to the skin or mucosa surfaces directly." The citation does not discuss injection or distinguish "applying" from "injecting."

Applicants' arguments do not address how to interpret the phrase. As such, one of skill would not be able to determine when they were infringing on the claim.

Claim 30 remains indefinite because the phrase and "method of claim 28, wherein the complex comprises a 5:1 ratio of polyethylenimine derivative nitrogen per DNA phosphate" is unclear. Claim 30 does not limit the complex to having polyethylenimine or polyethylenimine derivative; therefore, limiting the complex to having a 5:1 ratio of PEI nitrogen per DNA phosphate without first limiting the complex to one having PEI does not make sense because the complex can made with sugar (see claim 23). Furthermore, claim 30 refers to a 5:1 ratio of polyethylenimine derivative. It is unclear if applicants are attempting to limit the ratio or the compound used for gene delivery. Overall, the phrase is unclear.

Claim 31 remains indefinite because it is unclear whether the phrase "is formulated in a glucose solution" is limited to adding PEI, PEI-glu, PEI-gal, or PEI-man to a solution of glucose + water or if the phrase encompasses PEI-glu, PEI-gal, or PEI-man + water. The specification teaches PEI may be glycosylated (pg 21, Table 1) or solubilized in glucose (pg 22, line 35). Overall, it is unclear whether the phrase is limited to PEI or PEI derivative added to glucose + water or if the phrase encompasses adding PEI-glu to water. Applicants' arguments relating to "unexpected results" are moot because they do not address the indefiniteness of the phrase. Applicants argue both scenarios described by the examiner are encompassed by the phrase; however, it is not clear that PEI-glu added to water is "formulated in a glucose solution" because the glucose may stay attached to the PEI and not solubilize into the water.

Claim Rejections - 35 USC ' 102

4. Claims 23-26, 28, 30-32, 35, 37, 40 and 41 remain rejected and claim 43 is rejected under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000; 102(e) date=2-28-97) as supported by Carson (US Patent 5,679,647) for reasons of record.

Parent application 60/058,933 did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim 23). Therefore, claim 23 does not get priority back to parent application 60/058,933 (filed 9-15-97). Parent application 09/153,198 (filed 9-15-98) described complexing DNA with PEI-mannose in a 5-10% glucose solution on pg 26, lines 1-9. Therefore, claim 23 has priority to 9-15-98.

Behr taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). Luciferase is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Behr taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). Behr taught the DNA could encode an HIV peptide (col. 3, lines 57-67). The method of Behr inherently results in transfecting APCs because dendritic cells (a type of antigen presenting cell) are found in the epidermis (see definition of "dendritic cell", item 3). While not relied upon for the basis of the rejection, Carson provides evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the

skin transfects dendritic cells (col. 36-37, Examples 11-12). It is noted, however, the phrase "transfecting antigen presenting cells" in the preamble does not bear patentable weight in considering the art because the body of the claim does not require transfecting APCs.

Claims 25, 26 and 43 are included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are included because Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19). The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Applicants argue the luciferase gene is only a marker gene and is not used to raise or measure an immune response or transfect APCs. Applicants' argument is not persuasive. Luciferase is an immunogenic protein as claimed because it is foreign to the animal to which the gene delivery complex is applied. Furthermore, the claims do not require inducing an immune response. The method of Behr inherently results in

transfecting APCs because dendritic cells (a type of antigen presenting cell) are found in the epidermis (see definition of "dendritic cell", item 3).

Applicants argue Behr merely says the complex can be administered to the skin or mucosa without disclosing how to do so. Applicants' argument is not persuasive. Behr taught applying a gene delivery complex to the skin and need not demonstrate doing so to anticipate the claim. The step of applying the gene delivery complex in claim 23 has no limitation that distinguishes it from the step of applying taught by Behr.

Applicants argue the applicants have shown unexpected results and that Behr does not teach how to obtain a given result and only suggests performing a particular method. Applicants' arguments are not persuasive. The argument regarding unexpected results in misplaced under 102. Furthermore, the body of claim 23 does not require any given result that distinguishes it from the method taught by Behr. Finally, applying a gene delivery complex to the skin as taught by Behr inherently result in transfecting dendritic cells of the skin as supported by Carson.

Applicants argue the specification explicitly taught transfecting APCs. Applicants argue the phrase "transfecting antigen presenting cells" in the preamble of claim 23 should be given patentable weight because it "breaths life and meaning into the claim." Applicants argue the limitation "transfecting APCs" is directed to target cells having a specific function described on pg 11 and 12. Applicants' arguments are not persuasive.

The method of applying a gene delivery complex to the skin taught by Behr inherently results in transfecting dendritic cells as supported by Carson.

Applicants' argument regarding changing the method of Behr so as to render it inoperative has been considered (pg 18 of response). Applicants' argument is not persuasive. Behr taught applying a gene delivery complex to the skin of an animal. No changes to the step of applying are required, and the gene delivery complex taught by Behr is equivalent to the gene delivery complex in the method claimed.

Claim Rejections - 35 USC ' 103

The rejection of claims 23-26, 28, 30-32, 35, 38, 40 and 41 under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) in view of Adachi (J. Virol., 1986, Vol. 59, pages 284-291) and Owada (Microbiol. Immunol. Feb. 1998, Vol. 242, No. 2, pg 97-107) has been withdrawn. Claim 38 has been withdrawn because the NY5 and LAV strains of HIV taught by Adachi were not replication-defective (see title which describes the strains as "infectious"). Claim 23 and the other claims have been withdrawn because "to determine the immune response against the HIV antigens would occur *in vivo*" was inadequate motivation for one of ordinary skill to apply the infectious HIV taught Adachi to the skin of a non-human animal in view of Behr; and because one of ordinary skill would not have been motivated to apply the infectious, replication-competent HIV gene taught by Adachi to a human "to determine the immune response against the HIV antigens would occur *in vivo*". An obviousness rejection based on applying an infectious HIV to the skin of a non-human animal may exist, but would be superfluous at this time in view of the pending claims.

The rejection of claims 23-26, 28, 30-32, 35 and 37-41 under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) in view of Adachi (J. Virol., 1986, Vol. 59, pages 284-291), Owada (Microbiol. Immunol. Feb. 1998, Vol. 242, No. 2, pg 97-107) and Holler (US Patent 5,908,923) has been withdrawn in favor of the following rejection for clarity.

5. Claims 23-26, 28, 30-32, 35, 37-41 and 43 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) as supported by Carson (US Patent 5,679,647) and in view of Holler (US Patent 5,908,923).

Parent application 60/058,933 (9-15-97) did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim 23). Parent application 09/153,198 (9-15-98) described complexing DNA with PEI-mannose in a 5-10% glucose solution on pg 26, lines 1-9; therefore, claim 23 has priority to 09/153,198 (9-15-98).

Behr taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). Luciferase is an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Behr taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). Behr taught the DNA could encode a peptide from HIV (col. 3, lines 57-67). The

method of Behr inherently results in transfecting APCs because dendritic cells. Carson provides evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin transfects dendritic cells (col. 36-37, Examples 11-12). Case law established that reliance upon inherency in an obviousness rejection (103) instead of an anticipation rejection (102) is proper. In re Skoner, et al. 186 USPQ 80 (CCPA). It is noted, however, that the phrase "transfecting antigen presenting cells" in the preamble does not bear patentable weight in considering the art because it may not occur.

Claims 25, 26 and 43 are included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are included because Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19). The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (¶ bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Behr did not teach using a plasmid encoding a protein from a replication-defective, integrase-defective HIV.

However, Holler taught a plasmid encoding a replication-defective HIV that was integrase defective for use in vivo (col. 4, lines 51-54).

Thus, it would have been obvious for one of ordinary skill in the art at the time the invention was made to apply a gene delivery complex comprising a plasmid encoding an HIV protein to the skin/mucosa of an animal as described by Behr, wherein the plasmid encoded a replication-defective, integrase-defective HIV as taught by Holler. One of ordinary skill in the art would have been motivated to make the HIV replication-defective and integrase-defective to prevent causing disease in the animal.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, the desire to replace luciferase protein with an HIV protein was expressly taught by Behr. The desire to replace a plasmid encoding "an HIV peptide" taught by Behr with the plasmid encoding the replication-defective, integrase-defective HIV taught by Holler would not require hindsight reasoning. One of ordinary skill in 1997 would have recognized that an attenuated HIV such as the one described by Holler would prevent viral replication and death of the animal. One of ordinary skill in

the art would have also recognized that attenuated HIV was desirable in a lab setting to add an extra measure of safety for lab technicians in case of accidental exposure.

Applicants argue the examiner "refuses to give patentable weight to the phrase "transfecting antigen presenting cells" (pg 21). Applicants' argument is moot. The examiner provided reasoning why the method of Behr inherently results in transfecting APCs as claimed and case law that states that relying on inherency in an obviousness rejection is acceptable.

Applicants argue the examiner has merely pieced together the references to come up with motivation to experiment. Applicants' argument is not persuasive. The examiner has provided a specific plasmid encoding a replication-defective, integrase-defective HIV for use in the method of Behr and motivation for why one of ordinary skill would want to do so. "Motivation to experiment" is a mischaracterization of the motivational statements provided by the examiner; the motivational statement provided by the examiner is based on the desire to prevent HIV infection or death of the animal receiving or applying the gene delivery complex. Holler provides evidence for the desire to use a replication-defective, integrase-defective HIV to induce an immune response in an animal without causing infection or death.

Applicants argue Holler merely teaches that the replication-defective, integrase-defective HIV is usable in vivo but did not expressly use the HIV in vivo. Applicants' argument is not persuasive. Neither Behr nor Holler needs to provide examples of using the virus in vivo. Behr is being relied upon for the step of applying a plasmid encoding an HIV protein to the skin of an animal.

Applicants' argument in the paragraph bridging pg 26-27 appears to relate to the expectation of success. It appears that applicants are attempting to point out that some HIV vectors are "inefficient" at transfection. Applicants' arguments are not persuasive. First, transfecting inefficiently is still transfecting. Inefficient rates of transfection would not deter someone from using an HIV vector that prevents infection or death of the animal receiving or applying the gene delivery complex. Aurthur (Cancer Gene Res., 1997, Vol. 4, No. 1, pg 17-21) has not been considered because it has not been provided. Second, the combined teachings of Behr and Holler provide a reasonable expectation of successfully transfecting cells because Holler transfected CEM (a lymphoblastoid cell line) with integrase-defective HIV. Therefore, one of ordinary skill in the art at the time the invention was made would still have a reasonable expectation of successfully transfecting APCs using a plasmid encoding the HIV taught by Holler.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The following prior art remains of record but not relied upon because it is pertinent to applicant's disclosure:

The proceedings of the 3rd European conference on gene therapy of cancer, held from Sept. 11-13, 1997 at the University of Berlin, as supported by Diebold

(Advances in Experimental Med. and Biol., Oct. 1998, Vol. 451, pages 449-455). The preface of Advances in Experimental Med. and Biol., Oct. 1998, Vol. 451 (page v and vi) states that Vol. 451 contains the proceedings of the 3rd European conference on gene therapy of cancer. At the conference Diebold taught a complex comprising i) mannosylated PEI (PEI-man), and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter used to transfect dendritic cells via the mannose receptor (pg 452, line 10; pg 453, line 13-18). While Diebold described using a complex comprising PEI-man and DNA encoding an immunogenic protein at least a year and two days prior to the filing date of the instant application (Sept. 15, 1998), the conference was in Germany. 102(a) and (b) require that the information known in this country or published in this country or a foreign country prior. It does not appear that the information disclosed by Diebold was known in this country or published in any country until the publication of Advances in Experimental Med. and Biol., Vol. 451 in Oct. 1998. Therefore, the information disclosed by Diebold at the conference is not available under 102(a) or (b).

US Patent 6,420,176, application 09/153,198, claims a composition comprising DNA and mannosylated polyethylenimine, wherein said DNA encodes at least one immunogenic protein. The composition was restricted from the "method of using" the composition in application 09/153,198.

Song (PNAS, March 1997, Vol. 94, pg 1943-1948) injected retroviral particles encoding HIV IIIB env/rev to mice intramuscularly (pg 1943, col. 2, "Retroviral vectors"

and "Immunizations...") or dendritic cells transduced with the virus injected intraperitoneally (pg 1943, col. 2, "Retroviral vectors" and "Immunizations...").

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

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